REMARKS

Claim Objections

Claims 8-21 are objected to for failure to further limit the subject matter of a previous claim. From among the helpful possibilities suggested by the Examiner, applicants decided to cancel claims 8-21 and 28-41 since applicants are also in agreement with the Examiner that the structure of compounds is equivalent to the name of the compounds.

In view of the above amendment, withdrawal of the objection under 37 C.F.R. §1.75(c) is respectfully requested.

Double Patenting

Claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 42 and 43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5,750,104 in view of Sherman et al.;

Claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 42 and 43 are rejected under the same doctrine as being unpatentable over claims 1-4 of U.S. Patent No. 5, 324,514 in view of Sherman et al;

Claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 42 and 43 are rejected under the same doctrine over U.S. Patent No. 5,578,304 as being unpatentable over Sherman et al;

Claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 42 and 43 are rejected under the same doctrine over claims 1-10 of U.S. Patent No. 5,460,812 in view of Sherman et al;

As stated by the Examiner, none of these patents teach an enzyme composition having identical combination for the concentrations of components as the present application. None of the patents disclose using the claimed composition to treat IP-induced diarrhea or steatorrhea in HIV patients.

Applicants are now submitting herewith a Terminal Disclaimer under 37 C.F.R. §3.73(b) to obviate the double patent rejections of the specified claims along with the fee of $_____.

Withdrawal of the rejections is respectfully requested.

Claims Rejections – 35 U.S.C. §112

The essence of the rejection is that there is no disclosure that supports the prevention of PI-induced diarrhea or steatorrhea in HIV patients.

Applicants have now amended the claims to the reduction of diarrhea and/or steatorrhea in HIV-positive patients. The "preventing" of those conditions is now cancelled from the claims.

Withdrawal of the rejection is therefore respectfully requested.

Claims 1-8 are rejected under 35 U.S.C. §112, second paragraph, for reciting the limitation "colipase". The co-enzyme is a cofactor lacking antecedent basis in the claims.

Applicants have now amended the claims to include "cofactor". Based on this amendment, withdrawal of the rejection is respectfully requested.

Claim Rejections – 35 U.S.C. §103

Claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 41, 45 and 48 are rejected under 35 U.S.C. §103(a) as being unpatentable over Sipos (U.S. 5,750,1054) in view of Sherman et al. (2000).

The highlight of the rejection, as pointed out by the Examiner, is that Sipos does not teach that the disclosed composition can be used in combination with a protease inhibitor to treat PI-induced diarrhea or steatorrhea in HIB-positive patients.

However, Sipos does not teach that his composition can be used in combination with a protease inhibitor, and Sherman et al. take the "shotgun" approach by listing many medicaments for the treatment of PI-induces diarrhea, the combination of the two reference does not reach the level of obviousness to negate patentability.

Sherman et al. teach on page 909, second column, that:

> "Treatment of PI-associated diarrhea is largely nonspecific and anecdotal, ranging from over-the-counter remedies to prescription dugs such as pancreatic enzymes. Unfortunately, most of the available literature is published only in abstract form and centers around retrospective and survey data examining small numbers of patients. Comparisons are difficult to make between the studies because of inadequate descriptions of patient populations and differing grading systems for severity of diarrhea. In addition, most studies do not comment on whether patients were screened for enteric infections before initiation of anti-diarrheal therapy. The studies reported in these abstracts are summarized in Table 1. Because existing data are limited and inadequate to definitively determine optimal therapy, practitioners and patients need to work together to determine which treatment modality is appropriate based on efficacy, cost, and lifestyle. There appears to be an apparent emphasis on nelfinavir and saquinavir in the following studies; this is because most of the literature dealing with PI-associated diarrhea specifically addressed the treatment of diarrhea associated with these drugs. Diarrhea can be particularly problematic with these agents, and this fact probably led to the larger number of studies examining these agents."

Applicants claim a combination of High Activity Antiretroviral drugs in combination with an enteric-coated buffered composition with defined properties. This enteric coated buffered composition is not suggested by the Sherman et al. reference.

The rejection further states that Sherman et al. teach that PI-induced diarrhea in an HIV patient can be treated with medicaments containing pancreatic enzymes, such as Viokase and Ultrase. The rejection holds that it would have been obvious to administer the pancreatic enzyme compositions disclosed by the '104 patent to treat PI-induced diarrhea in HIV patients.

Applicants response to this rejection is as follows. Sherman et al. report that agents for which some efficacy has been shown for treatment of PI-associated diarrhea include oat bran, psyllium, loperamide, calcium carbonate, SP-303, and pancrelipase. Treatment of PI-associated diarrhea is "largely non-specific and anecdotal, ranging from over-the-counter remedies to prescription drugs such as pancreatic enzymes" (column 2, page 909, first full paragraph). Each of the commonly used medicaments for the treatment of diarrhea is discussed under separate headings: Oat Bran, Psyllium, Loperamide, Calcium, SP-303, Diphenoxylate/Atropine, and Pancrelipase. It appears from Table 1 (p. 910) that all the listed medicaments used against PI-associated diarrhea has some beneficial effects.

Based on the teachings of the reference, any of the above-listed medicaments could be experimented with to treat PI-induced diarrhea. However, experimentation is not a standard by which to judge patentability.

In a rejection under 35 U.S.C. §103, it is fundamental that all elements recited in a claim must be considered and given effect in judging the patentability of that claim against the prior art. See In re Geerdes, 491 F.2d 1260, 1262-63, 180 USPQ 789, 791 (CCPA 1974). Thus, a case of obviousness is established by showing that some objective teaching or suggestions in the applied prior art taken as a whole and/or knowledge generally available to one of ordinary skill in the art would have led that person to the claimed invention, including each and every limitation of the claims, without recourse to the reaching in appellants' disclosure. See generally In re Oetiker, 977 F.2d 1443 at 1447-48, 24 USPQ2d 1443 at 1446-47. The prior art as applied must be such that it would have provided one of ordinary skill in the art with both a suggestion to carry out applicant's claimed invention and a reasonable

expectation of success in doing so. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure". *Id.*

It is respectfully submitted that neither the suggestion or the expectation of success is contained in the cited Sherman reference.

Courts have repeatedly cautioned against employing hindsight by using the appellants' disclosure as a blueprint to reconstruct the claimed invention from the isolated teachings of the prior art. See, e.g., Grain Processing Corp. v America Maize-Products Co., 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988).

Going further in referring to applicant's composition, a pH of 7 to 9 is required in the small intestine to release the buffering agent from the enteric coated composition and rendering the lipase and colipase, biologically active. Such specificity is not suggested by the Sherman et al. reference.

The Examiner states that the term "composition" is a collection of items because a PI-inhibitor and a pancreatic enzyme are items that are together.

Applicants would like to note that in the Sherman et al. reference the pancreatic enzyme is administered per se, as it is, and is dissolved in the acidic environment of the stomach. Applicants' enteric coated enzyme along with the buffer does not dissolve in the stomach, it dissolves in the small intestine having a pH of 7 to 9. This pH is insured by the presence of a buffering agent in the enteric coated composition.

For the above-stated reasons, withdrawal of the rejection of claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 41, 45 and 48 is respectfully requested.

Claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 41, 45 and 48 are rejected under 35 U.S.C. §103(a) as being unpatentable over Sipos ('104) in view of Sherman et al., and further in view of Styver (U.S. 2003/0225029) and Hetherington et al., (U.S. 2003/003/0096274).

The Examiner states that U.S. Patent No. 5,750,104 contains pancreatic enzymes which have been successfully proven to treat diarrhea. The broadest reasonable interpretation of the term "composition" is a collection of items. The administration of a PI inhibitor and the pancreatic enzyme composition meets the limitation of a collection because the two medicaments are items that are together. Since medicaments containing pancreatic enzymes have been shown to be effective treatment for PI-induced diarrhea, the ordinary artisan would have had a reasonable expectation that any of the claimed composition could be used interchangeable with other pancreatic enzyme compositions to treat the ailment.

Regarding instant claims 43-48, drawn to a composition and method for correcting fat malabsorption and loss of body mass associated with diarrhea and/or steatorrhea, the treatment of diarrhea and/or steatorrhea will necessarily treat fat malabsorption and loss of body mass since diarrhea and/or stearorrhea are the cause of the associated symptoms.

Claims 1-6, 8-12, 22-26, 28-41 and 44-48 are rejected under 35 U.S.C. §103(a) as being unpatentable over Sipos (US 5,750,104) in view of Sherman et al. (2000) as applied to claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 44, 45 and 48 above, and further in view of Stuyver (US 2003/0225029) and Hetherington et al. (US 2003/0096274).

Sipose does not teach that the composition or method of use thereof, comprises a protease inhibitor that is a nucleoside reverse transcriptase inhibitor, as in claim 3, or a non-nucleoside reverse transcriptase inhibitor, as in claim 4.

Stuyver teaches that lamivudine and didanosine are standard anti-viral agents for the treatment of AIDS and that both substances can cause diarrhea in the patients (p. 4-5, Table 2).

Hetherington et al. disclose that abacavir is a standard anti-viral treatment for AIDS but that it has gastrointestinal side effects that include diarrhea (p. 2 section 0019 and p. 13, section 016).

Canani and Caskin et al. are cited to suggest the rejection .

Claims 1-3, 6-12, 22, 23, 26-32, 42-45 and 48 are rejected under 35 U.S.C. §103(a) as being unpatentable over Sipos (US 5,750,104) in view of Sherman et al. (2000) as applied to claims 1-3, 6, 8-12, 22, 23, 26, 28-32, 44, 45 and 48 above, and further in view of Canani et al. (1999) and Gaskin et al. (1982).

The combined disclosures do not teach a composition or method of use thereof having colipase.

Canani et al. disclose a medication trial for children with HIV with the intention of improving gastrointestinal function that had been negatively affected by protease inhibitor therapy. Initially, 30% (3 out of 10 subjects) had steatorrhea due to fat over-excretion in the feces. Canani et al. administered ritonavir with the protease inhibitors to ameliorate the side effects. Ritonovir improves the pharmacokinetics of drug metabolized by cytochrome P450 monooxygenase.

As to Canani, applicants would like to direct the attention of the Examiner to the following on page 309, second column and page 310, first column:

> "Intestinal dysfunction is a common feature of children with HIV infection. With other factors, it certainly contributed to the disease, by increasing the severity of malnutrition, and further compromising the existing immune impairment. The nature of intestinal involvement in HIV infection is still largely obscure. A role of opportunistic enteric agents, such as *Cryptosporidium* has been proposed (2). However, we did not find evidence of a relationship between intestinal dysfunction and cryptosporidiosis, the most frequent opportunistic infection in HIV-infected children (19). A direct role for HIV itself has been hypothesized, based on the presence of the virus in the intestinal tract, but this has not been confirmed (20-22). Finally, malnutrition, which is a common feature of advanced HIV disease, could itself be responsible for malabsorption."

The above quoted passage would not provide encouragement to one skilled in the art to combine the teachings of the reference with that of Sherman et al. reference.

Caskin et al. refer to the increase in lipase activity in the presence of colipase. Applicants acknowledge this fact, however, nothing is suggested in the reference to use colipase in the present invention in combination with an enteric-coated buffered composition.

Finally, applicants would like to comment on the newly amended claims in which it is specified that the HIV-positive patient drug is dissolved in the acidic environment of the stomach; and the buffered enteric-coated composition is being dissolved in the small intestine having a pH of 7 to 9. The present invention overcomes the drug-induced diarrhea.

The listing by the Examiner that lamivudine and didanosine to cause diarrhea in patients is not disagreed with by Applicants. Neither is that abacavir has gastrointestinal side effects that include diarrhea. However, Applicants' invention is not to describe what causes diarrhea and steatorrhea, but to treat these conditions. The references do not address what Applicants address, i.e., the treatment of these conditions.

For reasons of the above amendment and remarks, withdrawal of the rejections under 35 U.S.C. §103 over the references is respectfully requested.

Respectfully submitted,

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